57. The antigen composition of claim 55, wherein the tumor cells have an autologous HLA type on their cell surfaces.

58. The antigen composition of claim 55, wherein the tumor cells comprise UCLA-SO-M10, UCLA-SO-M24 and UCLA-SO-M101.

C3 cont'd

59. A method for treating cancer comprising administering to a patient in need of such treatment an amount of an antigen composition in accordance with any one of claims 55 through 58 that is effective to promote a cytotoxic or cytostatic effect against tumor cells of said cancer.

60. The method of claim 59, wherein the patient is a melanoma, sarcoma or carcinoma patient. --

REMARKS

I. Claims in the Case

Claim 18 has been canceled without prejudice. Claims 19 and 47 have been amended, and claims 48-60 added. Claims 19 and 47-60 are presently in the case.

II. Power of Attorney

Prosecution of the present case has been transferred to the undersigned representative. Enclosed is a new Power of Attorney. The undersigned Applicants' representative requests that all

future correspondences and communications regarding this case be directed as follows:

David L. Parker
Reg. No. 32,165
ARNOLD, WHITE & DURKEE
Box 4433
Houston, Texas 77210
(512) 320-7208

III. Amendments to the Claims

The claims have been amended in various ways to clarify the nature of the invention and to address the Examiner's § 112 and § 101 concerns.

Claim 47 has been amended and is now directed to an antigen composition comprising purified Urinary Tumor Associated Antigen (UTAA), wherein the UTAA is at least 0.6% of the total protein of the composition. Support for these amendments can be found in the specification, for example, at page 23, line 16-18.

New claim 49 depends from amended claim 47, and is directed to even more highly purified UTAA compositions wherein upon SDS-PAGE and silver staining, essentially only four bands having approximate apparent molecular weight of 138, 90, 50 and 25 kD are seen. This banding pattern is typically what is seen following purification of UTAA, *e.g.*, from serum (see, *e.g.*, page 36, lines 11-21).

New claim 51 is directed to banding pattern set forth in the specification at page 37, lines 1-5.

New claim 52 is directed to a more complex antigen composition which includes UTAA in combination with at least two

additional antigens selected from the group consisting of GM-2, GD-2, Fetal Antigen, and Melanoma-Tumor Associated Antigen (MTAA). Support for claim 52 and the claims depending therefrom (claims 52-57) can be found throughout the specification, *e.g.*, pages 16-17, 19-20, 22-23, 33-35, 52-56, and original claims 11-14.

Support for new claims 59 and 60 can be found in original claims 11-14, 16, and 17.

IV. Rejection of Claims 18, 19, and 47 Under 35 U.S.C. § 101 and § 112

The subject Official Action first enters rejections against all the pending claims under both 35 U.S.C. § 101 and § 112, first paragraph. It appears from these rejections that they are intended to set forth the same general concern, *i.e.*, the Examiner's position that the subject matter of the claims lack utility. For this reason, Applicants will address both of the pending rejections simultaneously.

In reviewing the rejections, it appears as though the Action's principal concern is with Applicants previous use of the word "vaccine." The Action takes the position that use of the word "vaccine" implied that for such a claim to have utility it must be demonstrated to protect from or treat disease, and it is insufficient to simply demonstrate that the antigens contained in the composition would be useful for other applications, such as in the preparation of antibodies which themselves have diagnostic value. Accordingly, Applicants have proceeded to amend the

claims and they are now directed to "antigen compositions" rather than "vaccines" *per se*.

It is submitted that this amendment should adequately address the Examiner's concern with respect to claims such as claims 19 and 47-53, in that these claims do not require or imply a successful cancer treatment. Accordingly, for these claims, it is submitted that sufficient utility lies in the fact that UTAA-containing antigen compositions are useful in the preparation of antibodies useful in cancer diagnosis.

In particular, in that the claims concern an antigen composition *per se*, the utility of these claims is satisfied by any utility, including in the preparation of diagnostic antibodies (see, *e.g.*, specification, page 23, line 7-10; page 28, line 29, to page 29, line 28; page 36, line 25, to page 37, line 7; and page 41, line 28, to page 44, line 11). Moreover, the *in vitro* diagnostic utility of the subsequent anti-UTAA antibody is demonstrated in the specification. Examples IX (pages 31-32) demonstrates preparation and carrying out of an assay for UTAA. Example XXVIII (pages 49-50) demonstrates the detection of UTAA in the urine of cancer patients -- only 2% false positives with almost 70% known positives identified. Lastly, Example XXIX (pages 50-51) demonstrates a relationship between UTAA and recurrence in the urine of cancer patients.

The only claims that raise a potential concern with respect to successful treatments of cancer are claims 54-59. It is respectfully submitted, however, that Applicants had previously

submitted data that is entirely adequate to support the utility of the subject matter of claims 54-59. Applicants direct the Examiner's attention to the previously submitted 1992 publication of the inventors entitled "Prolongation of Survival . . .", which demonstrates successful treatment of melanoma using the MCV of the invention. Moreover, this article demonstrates the surprising clinical efficacy of the claimed MCV vaccine in the prolongation of survival of cancer patients. It is submitted that this article clearly demonstrates the clinical efficacy of the MCV vaccine. For example, the reference, in its abstract, indicates that there has been no change in the prognosis for Stage IIIA and Stage IV melanoma patients in the last 20 years. Yet, in clinical trials, the MCV increased the median and 5-year survival of stage IIIA melanoma two-fold, and stage IV patient three-fold!! This is not only strong evidence of utility, but also strong evidence of non-obviousness, of the subject matter of claims 54 through 59.

For the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the utility rejections.

V. Rejection of Claims 18, 19, and 47 Under 35 U.S.C. § 102(b)

Next, the Action rejects claims 18, 19, and 47 as anticipated by the Gupta *et al.* 1987 abstract. The Examiner argues that Gupta *et al.* teaches the vaccination of melanoma patients with tumor cells, including M14 cells, and that such a

vaccine inherently must have included UTAA, in light of the Gupta *et al*. 1984 abstract.

First of all, the relevancy of the 1984 Gupta *et al*. abstract is unclear in that this reference is directed to MTAA (referred to therein as TAA), an entirely distinct antigen.

Nevertheless, Applicants point out that claim 47 requires the presence of UTAA in at least a partially purified form such that the UTAA is at least 0.6% of the total protein content of the composition. This is demonstrated in the specification to be a fairly substantial degree of purification, over and above the percentage of the UTAA antigen in tumor cells *per se*. For example, the Examiner's attention is directed to Example 1 on pages 22-23, wherein a procedure is set forth which resulted in a 105-fold enrichment of UTAA over its concentration in urine. At this degree of purification it was determined that UTAA was 0.6% of the total protein. The specification also provides techniques for even further purification of UTAA, for example, those set forth on pages 33-35. These techniques resulted in the realization of a very highly purified UTAA composition such that, when the composition was separated by SDS-PAGE and subsequent silver staining, only four bands were seen at molecular weights of 138, 90, 50, and 25 kD (see page 36, lines 11-21). As the Examiner is likely aware, the use of silver staining is perhaps the most sensitive of all techniques for detecting the presence of bands. Therefore, the demonstration of only four bands upon silver staining can be equated with a very highly purified

preparation, in terms of the percentage of the protein that is UTAA.

For the foregoing reasons, it is respectfully submitted that these claims clearly distinguish over the Gupta *et al.* abstract.

Claims 51-53 fall in a slightly different category, in that they do not require the presence of purified antigens *per se*. Regarding these claims, it is respectfully submitted that the 1987 abstract is in no way anticipatory. The abstract fails in any way to provide sufficient disclosure to allow one with skill in the art to reconstruct the vaccine to which in refers. For example, while it is true that the abstract refers to melanoma cell line M14, there is no direction provided as to how one with skill in the art would obtain such a cell line, and that the cell line selected should be one that provides the antigens referred to in the various claims -- Not all melanoma cell lines provide all of the required antigens![1] Moreover, the abstract provides no direction as to how one would use such a cell line in the preparation of an antigen composition within the scope of, for example, claim 51. Contrary to the Examiner's assertion, there is no teaching in either the 1987 or 1984 abstract that would lead one to conclude that UTAA is present on the surface of such a cell, and therefore, no direction for one to employ the cell in the preparation of a UTAA-containing antigen composition. It is again stressed that the reference to "tumor-associated antigen

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[1] In fact, only about 70 to 75% of the numerous melanoma cell lines screened to date have exhibited detectable quantities of UTAA.

(TAA)" in the 1984 abstract refers to MTAA not UTAA, and Applicants would be pleased to provide proof to this effect if needed.

The subject matter of claims 54-57 are even further removed from the Gupta *et al.* 1987 disclosure. For example, claim 54 requires a mixture of tumor cells and the presence of all five antigens, including UTAA, GM-2, GD-2, Fetal Antigen, and MTAA. Further, the claim requires that the antigens be present in amounts effective to promote a cytotoxic or cytostatic effect upon administration of the composition to a cancer patient. Similarly, claim 55 requires the use of live, irradiated tumor cells, and claim 57 requires all three of the preferred cell lines employed in Applicants' preferred vaccine.

Claims 58 and 59 require an effective cancer treatment, which is clearly in no way taught or suggested by the Gupta *et al.* abstract. In addition to the reasons discussed above, the 1987 abstract merely indicates an increase in anti-MTAA titre within three months of administering the vaccine which it discloses. However, there is no demonstration, and no results upon which to base a conclusion, that the vaccine resulted in a cytotoxic or cytostatic effect against the cancer. The Examiner must agree that a demonstration of successful treatment is truly surprising and unexpected.

For each of the foregoing reasons, it is respectfully submitted that Gupta *et al.* in no way anticipates (or obviates) the subject matter of the claims.

VI. Rejection of Claims 18 and 47 As Anticipated By Real *et al.*

Lastly, the Action rejects claims 18 and 47 as anticipated by the Real *et al.* patent, U.S. 4,562,160.

First of all, in that the Examiner has only rejected the composition claims, and not the method claim, it is presumed that the Real *et al.* patent is not being cited for the proposition that it discloses a vaccine that is useful in the treatment of cancer. Thus, Applicants will direct their comments simply to the composition claims that are pending.

Of the composition claims, it is respectfully submitted that only claims 47-49 are arguably relevant in that each of the remaining claims require fairly complex mixtures of antigens which are in no way taught by the Real *et al.* patent. Thus, Applicants will direct their comments to the subject matter of claims 47-49.

Although the Real *et al.* patent is very confusing in its presentation,[2] there are several features which demonstrate convincingly that the "90 kD" antigen with which it is concerned is entirely distinct from the subject matter of the present claims. For example, UTAA has an apparent molecular mass in the range of 590-620 kD under non-reducing conditions and an isoelectric point of 6.1. (See page 15, line 12-17.)

In contrast, the isolated "FD" antigen of Real *et al.* apparently exhibits a molecular weight of about 90 kD, whether

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[2] The Real *et al.* patent is also incomplete in that it refers to various figures and information that is, unfortunately, inexplicably not included in the specification.

determined under denaturing or non-denaturing conditions. Moreover, it has a distinct isoelectric point of 5.5 (col. 4, l. 61). A further distinguishing factor is the fact that out of 34 allogeneic melanoma cell lines, apparently only one was capable of absorbing FD serum (col. 4, l. 9-25; see also col. 4, l. 62-67). In contrast, UTAA has been found in about 70 to 75% of melanoma cell line tested.

For each of the foregoing reasons, it is respectfully submitted that Real *et al.* in no way teaches or suggests the subject matter of the claims.

VII. ATCC Deposit

Applicants will agree to deposit representative samples of the cell lines specified in the claims with the ATCC upon an indication of otherwise allowable subject matter.

VIII. Conclusion

The present response is intended to be a complete response to the referenced Official Action. If the Examiner has any questions or comments, or suggestion as to how to progress the

present case toward allowance, the Examiner is requested to contact the undersigned Applicants' representative.

Respectfully submitted,

David L. Parker
Reg. No. 32,165
(512) 320-7208

ARNOLD, WHITE & DURKEE
P. O. Box 4433
Houston, TX 77210

Attorney for Applicants

Date: March 31, 1994

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